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ADDENDUM FOR CHLOROFORM

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Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority Pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five jears. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. This addendum is to update the existing Ambient Water Quality Criteria Document for Chloroform.

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. Environmental Protection Agency is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under Contract No. 68-C8-0004.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CRAVE	Carcinogen Risk Assessment Verification Endeavor
DENA	Diethylnitrosamine
LOAEL	Lowest-observed-adverse-effect level
MCL	Maximum contaminant level
PEL	Permissible Exposure Limit
ppm	Parts per million
SGPT	Serum glutamic pyruvic transaminase
TLV	Threshold limit value
TWA	Time-weighted average

INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RfD = \frac{\text{NOAEL or LOAEL}}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RfDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multi-stage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on chloroform, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1987 to 1988). New key studies have been evaluated.

REVIEW OF NEW DATA

Toxicologic/Carcinogenic Effects

Several oral cancer studies have been reported since publication of the 1980 Ambient Water Quality Criteria Document for Chloroform (U.S. EPA, 1980).

Jorgenson et al. (1985) maintained groups of 50-330 male Osborne-Mendel rats and groups of 50-430 female B6C3F1 mice on drinking water containing chloroform at concentrations of 0, 200, 400, 900 or 1800 mg/l for 104 weeks. Assuming a linear relationship between tumor incidence and dose, group sizes were adjusted to detect a tumor response at low doses. Thus, the low dose groups had more animals. A dose-related decrease in water consumption occurred in both rats and mice. Based on water consumption data and body weight changes, the investigators calculated TWA chloroform dosages of 0, 19, 38, 81 and 160 mg/kg/day for rats and 0, 34, 65, 130 and 263 mg/kg/day for mice. There was a statistically significant ($p<0.0001$ by Peto trend test) dose-related increased incidence of all kidney tumors, of renal tubular adenomas and of renal tubular adenoma and/or adenocarcinoma in male rats. The incidence of adenomas was 4/301 in controls, 2/313 at 19 mg/kg/day, 3/148 at 38 mg/kg/day, 2/48 at 81 mg/kg/day and 5/50 at 160 mg/kg/day. The incidence of adenoma and/or adenocarcinoma was 4/301 in controls, 4/313 at 19 mg/kg/day, 4/148 at 38 mg/kg/day, 3/48 at 81 mg/kg/day and 7/50 at 160 mg/kg/day. The incidences of adenoma and of adenoma and/or adenocarcinoma at the highest dose were significantly higher than controls ($p<0.01$). No evidence of carcinogenicity was observed in female B6C3F1 mice. The lack of a carcinogenic response in female B6C3F1 mice contrasts with the results of the NCI (1976) study, which found increased incidences of liver tumors in both sexes of B6C3F1 mice treated by gavage with chloroform in corn oil.

The differences may have been due to the different dosing regimens (gradual administration in drinking water vs. bolus in gavage) or the different vehicle (water vs. corn oil).

Palmer et al. (1979) found no evidence of carcinogenicity in Sprague-Dawley rats treated by gavage with chloroform in toothpaste. In one experiment, groups of 25 male and 25 female rats were given doses of 15, 75 or 165 mg/kg/day and groups of 75 males and 75 females were given the vehicle alone 6 days/week for 52 weeks. In a second experiment, groups of 50 male and 50 female rats were given 0 or 60 mg/kg/day 6 days/week for 80 weeks, followed by a 15-week observation period.

Tumasonis et al. (1985, 1987) found increased incidences of neoplastic nodules and hepatic adenofibrosis in the livers of Wistar rats treated with chloroform in the drinking water for their lifespans. Treated groups consisted of 32 males and 45 females receiving drinking water containing 2900 ppm chloroform for 72 weeks followed by 1450 ppm for the remainder of the lifetime. Of these, 28 males and 40 females were necropsied. Controls consisted of 26 males and 22 females. Of the control rats, 22 males and 18 females were necropsied. Only the livers and other organs with grossly observable lesions were examined histologically. The incidence of neoplastic nodules was significantly ($p<0.03$) increased in treated females (10/40 or 25%) compared with female controls (0/18). The incidence of hepatic adenofibrosis was significantly increased ($p<0.001$) in treated males (17/28 or 61%) compared with control males (0/22) and in treated females (34/40 or 85%) compared with control females (0/18).

In three separate experiments, Roe et al. (1979) administered chloroform to four different strains of mice by gavage, 6 days/week for 80 weeks, followed by a 13- to 24-week observation period. In the first experiment,

groups of 52 male and 52 female ICI mice received toothpaste containing chloroform at 17 or 60 mg/kg/day, and 104 mice/sex served as controls. In the second experiment, groups of 52 male ICI mice received toothpaste containing chloroform at 0 or 60 mg/kg/day. In the th d experiment, groups of 52 male mice of strains C57Bl, CBA, CF/1 and ICI received 0 or 60 mg chloroform/kg/day in toothpaste or in arachis oil. No increased incidences of tumors were observed in C57Bl, CBA or CF/1 mice. In ICI mice treated with chloroform in toothpaste, males, but not females, had an increased incidence of epithelial tumors of the kidney at 60 mg/kg/day (8/38), but not at 17 mg/kg/day (0/37), compared with controls (0/72). A more pronounced increase in kidney tumor incidence was observed in male mice given 60 mg/kg/day in arachis oil (12/48 treated vs. 1/50 controls). The incidence of malignant kidney tumors in these mice was 0/50 in controls and 9/48 in the 60 mg/kg/day group.

Klaunig et al. (1986) tested chloroform as a whole carcinogen and as a tumor promoter in B6C3F1 male mice. Groups of 35 mice received either plain drinking water for $\leq$56 weeks, drinking water containing DENA for 4 weeks followed by plain drinking water for $\leq$52 weeks, plain drinking water for 4 weeks followed by drinking water containing chloroform at 600 or 1200 mg/l for $\leq$52 weeks, or drinking water containing DENA for 4 weeks followed by drinking water containing chloroform for $\leq$52 weeks. Ten mice/group were sacrificed after 24 weeks and the remaining 25 mice/group were sacrificed after 52 weeks. Comprehensive gross examination and histological examination of liver, lungs and kidneys were performed on all mice that were sacrificed or that died during the experiment. None of the untreated controls died. Deaths of chloroform treated mice occurred between weeks 40 and 52 as follows: four mice treated with DENA and 1200 mg chloroform/l, three mice

treated with DENA and 600 mg chloroform/ℓ, three mice treated with 1200 mg chloroform/ℓ alone and two mice treated with 600 mg chloroform/ℓ alone. Liver tumors were found in 0/10 untreated controls at 24 weeks and 5/25 controls at 52 weeks. No statistically significant increased incidence of liver tumors was found in the mice treated with chloroform without initiation with DENA. In mice treated with chloroform at either dose following initiation with DENA, there was a significant decrease in the number of liver tumors per mouse compared with the group initiated with DENA followed by plain drinking water.

Pereira et al. (1985) also found an apparent inhibition of the development of liver tumors in male Sprague-Dawley rats treated by gavage with chloroform in drinking water following initiation with DENA.

Heywood et al. (1979) studied the effects of chloroform in dogs. Chloroform in toothpaste in gelatin capsules was administered to groups of eight male and eight female beagles at 15 or 30 mg/kg/day, and groups of 16 males and 16 females were given the vehicle alone, 6 days/week for 7.5 years. No significant changes were found in body weight, food and water consumption, organ weights, hematology or clinical chemistry parameters. SGPT was slightly elevated for the first 5 years, and the incidence of fatty cysts in the liver was slightly increased at both doses, compared with controls. There was no carcinogenic response.

The drinking water study in rats by Jorgenson et al. (1985) supports the results of the NCI (1976) study, which found that chloroform administered in corn oil by gavage to Osborne-Mendel rats resulted in increased incidences of renal tumors. In both studies, the primary tumors were of tubular cell origin appearing at similar times. In addition, renal tumors occurred in

ICI mice treated by gavage with chloroform in a toothpaste base in the study by Roe et al. (1979). When the vehicle was arachis oil, the renal tumor response was enhanced.

Regarding liver tumors in mice, the data are conflicting. Jorgenson et al. (1985) found no carcinogenic response in female B6C3F1 mice administered chloroform in drinking water, and Roe et al. (1979) found no increases in liver tumors in four strains of mice treated by gavage with chloroform in toothpaste or in arachis oil. The NCI (1976), however, did find increased incidences of liver tumors in both male and female B6C3F1 mice given chloroform in corn oil by gavage. In a subchronic 90-day study, Bull et al. (1986) found that chloroform administered by gavage to male and female B6C3F1 mice was more hepatotoxic when the vehicle was corn oil than when administered in an aqueous vehicle. Thus, it appears that corn oil may enhance the hepatotoxicity and hepatic carcinogenic effects of chloroform in mice.

No epidemiologic studies have evaluated oral exposure to chloroform by itself. Several studies have been published, however, regarding populations which utilize chlorinated drinking water in which chloroform is the predominant chlorinated hydrocarbon compound. These studies as well as several occupational studies have been extensively reviewed by the U.S. EPA (1985a). The results of these studies are corroborated by a recent article by Cantor et al. (1987) in which an increased risk of bladder cancer due to the consumption of chlorinated surface waters was reported. This study compared 2805 cases with 5258 controls according to consumption of chlorinated surface water. Women and nonsmokers of both sexes had an increased risk of bladder cancer associated with duration of exposure to chlorinated surface water. The odds ratio for the highest vs. the lowest

quintile served by a chlorinated surface water source was 1.7 among subjects with 49-50 years exposure and 2.0 for those with ≥60 years exposure. When only nonsmoking respondents with exposure to chlorinated surface waters above the population median were compared with nonchlorinated groundwater users, the odds ratio increased with exposure duration to 3.1 for those individuals with ≥60 years exposure.

The U.S. EPA (1985a) concluded that because other possible carcinogens were present along with chloroform in chlorinated surface waters, it is impossible to identify chloroform as the sole carcinogenic agent in epidemiologic studies made of populations with chlorinated drinking water. Therefore, the epidemiologic evidence for chloroform's carcinogenicity must be termed inadequate.

It is generally accepted that the carcinogenic activity of chloroform identified in animal experiments resides in its highly reactive intermediate metabolites such as phosgene. There is no evidence that qualitative differences in the metabolic pathways on metabolite profiles exist between mice, rats and humans. Chloroform has been classified by the U.S. EPA (1987) as a Group B2 carcinogen, meaning that while there is no or inadequate evidence of carcinogenicity in humans, the animal evidence is sufficient to suggest a carcinogenic potential in humans beings.

Bioconcentration Factor (BCF)

Pertinent new information concerning the bioconcentration factor for chloroform is currently undergoing Agency review. The BCF value of 3.75 determined in U.S. EPA (1980) will be used until that review has been completed.

QUANTIFICATION OF EFFECTS

The Ambient Water Quality Criteria Document for Chloroform (U.S. EPA 1980) used a q_1^* of 0.18272 $(mg/kg/day)^{-1}$ estimated from the dose-response data for liver tumors in female mice in the NCI (1976) study and a BCF of 3.75 to derive the following criteria corresponding to increased lifetime cancer risk levels of 10^{-7}, 10^{-6} and 10^{-5}: 0.019, 0.19 and 1.90 µg/ℓ, respectively, for consumption of water and fish and shellfish and 1.57, 15.7 and 157 µg/ℓ, respectively, for consumption of fish and shellfish alone. More recently, Jorgenson et al. (1985) found that chloroform administered in drinking water to rats produced increased incidences of renal tubular adenomas and adenoma and/or adenocarcinoma. This assay was designed for detection and quantitation of effects at low doses, used large numbers of animals at the low doses, and continued treatment for the lifetime of the animals. Therefore, the U.S. EPA (1987) considered the study by Jorgenson et al. (1985) a more appropriate basis for the derivation of an oral carcinogenicity assessment for chloroform and verified a q_1^* of 6.1×10^{-3} $(mg/kg/day)^{-1}$ for oral exposure based on the incidence of kidney tumors in male rats observed in this study.

Using the verified q_1^* of 6.1×10^{-3} $(mg/kg/day)^{-1}$, and assuming 70 kg body weight and a daily intake of 2 ℓ of water and 6.5 g of fish and

shellfish with a BCF for chloroform of 3.75, the criteria for chloroform in ambient water are as follows:

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (µg/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g fish and shellfish	0	0.57	5.7	57	570
Consumption of fish and shellfish only	0	47	470	4700	47,000

EXISTING STANDARDS AND CRITERIA

The OSHA PEL for chloroform is 50 ppm in the workroom air (OSHA, 1985). ACGIH (1988) adopted a TWA-TLV of 10 ppm for chloroform with a designation of A2 (i.e., a suspected human carcinogen).

The verified slope factor for inhalation exposure to chloroform is 8.1×10^{-2} $(mg/kg/day)^{-1}$ (U.S. EPA, 1987). The chloroform levels in air associated with incremental increases of cancer risk of 10^{-5}, 10^{-6} and 10^{-7} are 4.3×10^{-4}, 4.3×10^{-5} and 4.3×10^{-6} mg/m^3, respectively.

The verified slope factor for oral exposure from drinking water is 6.1×10^{-3} $(mg/kg/day)^{-1}$ (U.S. EPA, 1987). Chloroform is classified in U.S. EPA Group B2; probable human carcinogen (U.S. EPA, 1987).

An interim MCL of 0.1 mg/ℓ for total trihalomethanes in drinking water is proposed based on chronic toxicity data for chloroform and existing technology and treatment methods (U.S. EPA, 1988).

The verified chronic oral RfD is 0.01 mg/kg/day based on the Heywood et al. (1979) study (U.S. EPA, 1985b).

An RQ of 10 pounds is proposed for chloroform based on potential carcinogenicity (U.S. EPA, 1988).

The FDA approved chloroform for use as an indirect food additive (i.e., a component of articles that may come in contact with food). It has been exempted from tolerance when used as a solvent in pesticide formulations applied to crops. The FDA has restricted its use in drugs and cosmetic products as a result of the positive NCI (1976) bioassay (U.S. EPA, 1985a).

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1988. Threshold Limit Values and Biological Exposure Indices for 1987-1988. Cincinnati, OH. p. 15.

Bull, R.J., J.M. Brown, E.A. Meierhenry, T.A. Jorgenson, M. Robinson and J.A. Stober. 1986. Enhancement of the hepatotoxicity of chloroform in B6C3F1 mice by corn oil: Implications for chloroform carcinogenesis. Environ. Health Perspect. 69: 49-58.

Cantor, K.P., R. Hoover, P. Hartge, et al. 1987. Bladder cancer, drinking water source, and tap water consumption: A case-control study. J. Natl. Cancer Inst. 79: 1269-1279.

Heywood, R., R.J. Sortwell, P.R.B. Noel, et al. 1979. Safety evaluation of toothpaste containing chloroform III. Long-term study in beagle dogs. J. Environ. Pathol. Toxicol. 2: 835-851.

Jorgenson, T.A., E.F. Meierhenry, C.J. Rushbrook, R.J. Bull and M. Robinson. 1985. Carcinogenicity of chloroform in drinking water to male Osborne-Mendel rats and female B6C3F1 mice. Fund. Appl. Toxicol. 5: 760-769.

Klaunig, J.E., R.J. Ruch and M.A. Pereira. 1986. Carcinogenicity of chlorinated methane and ethane compounds administered in drinking water to mice. Environ. Health Perspect. 69: 89-95.

NCI (National Cancer Institute). 1976. Report of carcinogenesis bioassay of chloroform. NTIS PB-264 018.

OSHA (Occupational Safety and Health Administration). 1985. Permissible Exposure Limits. 29 CFR 1910.1000.

Palmer, A.K., A.E. Street, F.J.C. Roe, A.N. Worden and N.J. Van Abbe. 1979. Safety evaluation of toothpaste containing chloroform II. Long term studies in rats. J. Environ. Pathol. Toxicol. 2: 821-833.

Pereira, M.A., L-H.C. Lin, J.M. Lippitt and S.L. Herren. 1985. Trihalomethanes as initiators and promoters of carcinogenesis. Environ. Health Perspect. 46: 151-156.

Roe, F.J.C., A.K. Palmer, A.N. Worden and N.J. Van Abbe. 1979. Safety evaluation of toothpaste containing chloroform I Long-term studies in mice. J. Environ. Pathol. Toxicol. 2: 799-819.

Tumasonis, C.F., D.N. McMartin and B. Bush. 1985. Lifetime toxicity of chloroform and bromodichloromethane when administered over a lifetime in rats. Ecotoxicol. Environ. Saf. 9: 233-240.

Tumasonis, C.F., D.N. McMartin and B. Bush. 1987. Toxicity of chloroform and bromodichloromethane when administered over a lifetime in rats. J. Environ. Pathol. Toxicol. Oncol. 7(4): 55-63.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Chloroform. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-033. NTIS PB117442.

U.S. EPA. 1985a. Health Assessment Document for Chloroform. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA/600/8-84/004F. NTIS PB86-105004.

U.S. EPA. 1985b. Integrated Risk Information System (IRIS). Reference Dose (RfD) for Oral Exposure for Chloroform. Online. (Verification date 12/2/85). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1987. Integrated Risk Information System (IRIS). Carcinogenicity Assessment for Lifetime Exposure to Chloroform. Online. (Verification date 8/26/87). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1988. Integrated Risk Information System (IRIS). Chemical File for Chloroform. Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.